WORLD INTELLECTUAL PROPERTY ORDANIZATION International Bureau

WO 94/12463 9 June 1994 (09.06.94) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT) (11) International Publication Number: (43) International Publication Date: **4**1 (51) International Patent Classification 5:

PCT/EP93/03193 COTC 20304, A61K 31/21, COTD 333/22, 209/46, 491/04, A61K 31/40, 31/38, COTD 207/337, 209/88, 333/24, A61K 31/16, COTC 235/78, 235/34, 233/21 (21) International Application Number:

(81) Designated States: AU, BR, CA, CZ, Fl. HU, Jr. RP, KR, RN, NO, NZ, PL, RO, RU, SK, UA, US, European patent (AT, BR, CH, DE, DK, ES, FR, GB, GR, E, IT, LU, MC, NI, PT, SB). (22) International Filing Date: 15 November 1993 (15.11.93)

Published With international search report E (71) Appirent (for all designated Scattes are spt US); HCT-HEALTH CANE TRADING LTD. [IE/IE]; Dame Street, Dublin 2-(IE). 26 November 1992 (26.11.92)

(30) Priority Date: MI92A002699

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Nitric esters with pharmacological activity having general formula (f), their pharmaceutical utilisation and process for their preparation. (57) Abstract

(54) THE: NITRIC ESTERS HAVING A PHARMACOLOGICAL ACTIVITY AND PROCESS FOR THEIR PREPARATION

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NITRIC ESTERS HAVING A PHARMACOLOGICAL ACTIVITY

AND PROCESS FOR THEIR PREPARATION

Object of the present invention are nitric esters with an anti-inflammatory and/or anti-platelet aggregation activity, their pharmaceutical utilization and the process for their preparation.

PRIOR ART

ce 2-(-3-benzoylphenyl)propionic acid, commonly known Some derivatives of propionic acid, such as for instanas ketoprofen, have been used for a long time as pharmaceutical preparations for their anti-inflammatory activity and are sold on the different international 2-(3-benzoylphenyl)propionic acid has been corresponding to the US patent 3,641,127; in the French PINNA et al., FARMACO Ed. Sci. 35,684 (1980); while the markets since many years. The process for the preparain the South African patent n° 68 00,524, patent n° M6444 and also in C.A. 75,5528m (1971); G.A. pharmacokinetics in humans is described in T. ISHIZAKI et al., Eur.J.Clin. Pharmacol. 18,407 (1980). The use ce, keptofren, as well as the use of other products which are utilized as anti-inflammatory agents, involreactions, for instance in the gastrointestinal apparatus, as well as possible of derivatives of propionic acid, such as, for instandamages to the liver and the kidneys. ves, as known, severe adverse described ŏ

There is much experimental evidence [S. MONCADA, R.M.J.PALMER, E.A.HIGGS, Pharmacological Reviews,

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. N 43(2), 109 (1991); T.H.LUSHER, C.M.BOULANGER, Y.DOHI, Z.YANG, Hypertension, 19,117 (1992)], on whose basis the integrity of vasal endothelium is thought to be a basic barrier against the onset of pathological processes in several organs and apparatuses.

Such protection barrier, and therefore the integrity of the vasal endothelium, is ensured physiologically by the presence of nitric oxide and prostacyclin.

The treatment with non steroid drugs having an anti-inflammatory activity, such as, for instance, 2-(3-benzoylphenyl)propionic acid or ketoprofen, causes the inhibition of cyclo-oxygenase, an enzyme which syntesizes the precursor of prostacyclin.

As a consequence, having so inhibited the production of prostacyclin, the reserve of same in the tissues is markedly depauperated, and therefore the integrity of vasal endothelium is compromised.

As said, because of this endothelial damage due to the reduction of prostacyclin, diffuse pathological process break out which affect the gastrointestinal apparatus, liver and kidneys.

OBJECTS OF THE INVENTION

Object of the present invention is that to provide a group of products which, while ensuring the maintenance of the pharmacological activity characteristic of the known anti-inflammatory agents, are capable of eliminating the adverse reactions caused by the treatment with

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said agents.

products having an anti-inflammatory activity while tion of a process for the preparation of a group of Another object of the present invention is the realizabeing exempt from the adverse reations which are typical of anti-inflammatory agents.

DESCRIPTION OF THE INVENTION

These and still other objects and associated advantages which will appear from the following description, are obtained with nitric esters having the following general formula:

substituted or non substituted alkyl chains, R is A and B are chosen among hydrogen, linear or branched, chosen among

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(IXX)

 R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 1 to 12 carbon atoms, substituted or non substituted, Y is chosen among oxygen, NH, NR $_1$, where R_1 is a linear or branched alkyl group and n is comprised between 1 and 10.

In fact, it has been observed that the introduction of a group such as a terminal nitric ester in the general formula derivatives (I) allows to mantain the pharmacological activity characteristic of non steroid anti-inflammatory agents, while eliminating the adverse reactions caused by the treatment with such agents.

Besides, it has been observed that derivatives (I) are useful also in the treatment of various morbide conditions, such as, for instance, rheumatic diseases in general, disoders of immunologic nature, and can also assuage light-middle severity painful conditions of any

More still, the derivatives (I) subject matter of this invention, are useful in the treatment of diseases of the cardio-vascular apparatus, and in particular in the treatment of miocardial and brain ischemiae as well as in artery thrombosis as anti-platelet aggregation agents.

Always according to this invention, a nitric ester of general formula (I) proved particularly advantageous, where:

hydrogen is chosen as A and B, methyl is chosen as R_2 ,

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and as R is chosen

(IV)

oxygen is chosen as y and n is equal to four, according to the following formula:

Also particularly advantageous according to this invention is the nitric ester of a general formula (I) where:

hydrogen is chosen as A and B, as R is chosen

(XX)

methyl is chosen as $\rm R_2$ oxygen is chosen as Y and n is equal to four, according to the following formula:

Still more, always according to the present invention, particularly advantageous are the nitric esters of general formula derivatives (I) where:

hydrogen is chosen as A and B, as R are chosen

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(VIII)

methy1, ethy1 and hydrogen are chosen as \mathbf{R}_2 , oxygen is chosen as y and n is equal to four, according to the

following formulae:

For the preparation of general formula nitric esters to the invention, comprises the following (I), subject matter of the present invention, particua first process which, larly advantageous proved to be according steps:

- Preparation of the sodium salt of the products having the following general formula:

(XIX)

where R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, R is chosen among: (II), (III), (IV), (VI), (VII), (VIII), (X), (xxx), (xxxv)

or preparation of derivatives (XIV) functionalized to the carboxyl group, such as acilic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (XIV) or between said derivatives (XIV) functionalized to the carboxylic group, with a composition having the following general formula:

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(X

where:

 R_{4} is chosen among chlorine, bromine, NHR $_{6}$ with R_{6} substituted or non substituted alkyl chains, $R_{
m 3}$ is chosen among chlorine, bromine, and iodine, and n is comprised between 1 and 10, obtaining in this way the chosen among hydrogen, lineal or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, relative monomeric esters or the relative amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, obtaining in this way nitric esters of derivatives (I).

Also a second process proved to be particularly advantageous which, always according to the present invention, comprises the following steps: - Preparation of the sodium salt of derivatives having the following general formula:

where R is chosen among:

(II), (III), (IV), (VI), (VII), (VIII), (IX), (X), (XXX), (XXXV)

R₂ is chosen among hydrogen, methyl, ethyl, alkyl preparation of derivatives (XIV) functionalized to the carboxylic group, such as acidic chlorides, anhydrides substituted or non substituted, or, alternatively, chains linear or branched by 3 to 12 carbon atoms,

- Reaction between the sodium salt of said derivatives (XIV) or between said derivatives (XIV) functionalized to the carbboxylic group, with a composition having the following general formula:

 $R_{f 4}$ is chosen among chlorine, bromine, NHR $_{f 6}$ with $R_{f 6}$ substituted or non substituted alkyl chains, and n is equal to hydrogen, or linear or branched alkyl chain, A comprised between 1 and 10, obtaining in this way the and B are chosen among hydrogen, linear or branched, relative monomeric esters or amides;

- Reaction of said monomeric esters or said amides with

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obtaining in this way said monomeric esters or said amides characterized by the presence of a terminal an halogenating composition such as PBr₃ or the like, halogen group;

characterized by the presence of a terminal halogen group, with a nitrating agent such as AgNO₃ or the - Reaction of said monomeric esters or said amides like, obtaining in this way nitric esters of derivatiThe solvents utilized in the processes subject matter of this invention are preferably chosen among chloroform, methylene chloride, acetonitrile, dimethylformamide, tetrahydrofuran, 1,4-dioxane and the like.

subject matter of this invention, consist of a limited number of steps, allowing to obtain the products which derive from said processes in a short time and with The processes for the preparation of derivatives (I) satisfactory yields even on the industrial plane.

According to the processes subject matter of this invention, the preparation of a nitric ester having the following formula:

red as described in the following example, given as a proved to be particularly advantageous, which is prepamere indication without limiting the protection scope of this invention.

EXAMPLE 1

в) 2 g of 2-fluoro-alpha-methyl-4-diphenylacetic acid were added to a solution constituted by 10 ml of methyl stirred for 5 minutes, then the solvent was evaporated under reduced pressure, obtaining the sodium salt of 2-fluoalcohol and 0.23 g of Na. The reaction mix was ro-alpha-methyl-4-diphenylacetic acid.

lacetic acid obtained in this way was suspended in 20 b) The sodium salt of 2-fluoro-alpha-methyl-4-dipheniml of dimethylformamide and 3 ml of 1,4-dibromo-butane The reaction mix was stirred for 22 hours at room temperature, then the NaBr which had formed was filtered and the solvent was evaporated under reduced pressure. The residue so obtained was treated with methylene chloride and, after elimination by filtration of the insoluble residue, the re, obtaining 3 g of a dry residue which was purified by silica gel chromatography, utilizing an eluent mix methylene chloride was evaporated under reduced pressuconstituted by hexane/methylene chloride 1/1 (V/V). were added by dripping to this suspension.

fluoro-alpha-methyl-4-diphenylacetate of 4-bromobutyl the solvent was evaporated under reduced pressure and 1.86 g of The head fractions were collected,

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XXII) were obtained

IR (cm-1): C=0,1470

1-H-NMR (300 MHz) (CDCl3) : 1.51ppm (d,3H); 1.56ppm (m,4H); 3,35ppm (t,2H); 3.61ppm (q,1H); 4.1ppm (t,2H); 7.3-7.55 (s, 1H); (m,1H); 7.17ppm 7.05ppm

c) 1.2 g of AgNO $_{
m J}$ dissolved in 8.3 ml of acetonitrila under b) dissolved in 7.5 ml of acetonitrile. The reaction mix was stirred for 48 hours at room temperature and then filtered. The solvent was evaporated from the resulting solution under reduced pressure, obtaining a residue which was treated with methylene chroride. The mix obtained in this way was filtered again and the organic phase was purified by silica gel pressure chromatography, utilizing an eluent mix constituted by diethylether/hexane 3/7 (V/V). The fractions containing as described the products were collected, the solvent was evaporated under reduced pressure and 1.2 g of nitric ester of 2fluoro-alpha-methyl-4-diphenyl acetate of 4-hydroxybuwere added to 1.86 g of (XXII), obtained tyl (XII) were obtained.

 $IR(cm^{-1}): C=0,1737; ONO_2, 1623, 1274.$

¹H-NMR (300 MHz) (CDCL₃): 1.53ppm (d,3H); 1.72ppm (t,2H); (m,4H); 3.74ppm (g,1H); 4.13 ppm (t,2H); 4.4ppm 7.13ppm (t,2H, aromatics); 7.32-7.42ppm (m,4H, tics); 7.53ppm (m,2H, aromatics). Mass spectrometry (i.e.): $(M^{+})361$; $(M+1-NO_{2})316$; 243;

199.

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester having the following formula:

proved particularly advantageous, which is prepared as described in the example shown hereunder, given as a mere indication without limiting the protection scope of this invention.

and 1.19 g of Na. The reaction mix was stirred for 15 minutes, then the solvent was evaporated under reduced pressure, obtaining a residue constituted by the sodium a) 10 g of 2-(3-benzoilphenyl)propionc acid were added of methyl alcohol salt of 2-(3-benzoilphenyl)propionic acid. to a solution constituted by 80 ml

way. The reaction mix was kept for 24 hours at room temperature and then the solvent was evaporated under mo-butane were added to the residue obtained in this reduced pressure. 40 ml of water and 60 ml of methylene b) 100 ml of dimethylformamide and 28.1 g of 1,4-dibro-

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chloride were added to the residue obtained in this way and the organic phase was extracted and anhydrified on was evaporated under reduced pressure until a dry residue was obtained. the solvent sodium sulphate and

ted, the solvent was evaporated under reduced pressure The residue was purified by silica gel chromatography, ether/hexane 1/1 (V/V). The head fractions were collecand 8.8 g of 2-(3-benzoilphenyl)propionate of 4-bromoģ mix constituted butyl (XXIII) were obtained. utilizing an eluent

'H-NMR(200МН2) (CDC13): 1.53ррm (d,3H); 1.84ррm (m,4H); 3.32ppm (t,2H); 3.78ppm (q,1H); 4.09ppm (t,2H); 7.27 (m,1H, aromatics); 7.38-7.99 (m,8H aromatics).

Mass spectometry (i.e.): 388 (M⁺); 309 (M⁺-Br); 209.

c) 5.5 g of AgNO₃ dissolved in 18 ml of acetonitrile were added to 8.8 g of (XXIII) obtained as described tion mix was stirred for 24 hours at room temperature and, having added 1.76 g of AgNO $_{
m 3}$, the reaction mix was stirred for 24 more hours at room temperature and then filtered. The solvent was evaporated from the resulting under b) dissolved in 35 ml of acetonitrile. The reacobtaining a residue which was treated with methylene chloride. solution under reduced pressure,

the mix obtained in this way was filtered again and the pressure chromatography, utilizing an eluent mix constituted by gel silica organic phase was purified by ethyl ether/hexane 3/7 (V/V)

the solvent was evaporated under reduced pressure and 3.4 g of nitric ester of 2-(3-benzoilpheny1) propionate The fractions containing the product were collected, of 4-hydroxybutyl (XVIII) were obtained.

IR (cm^{-1}) : C=0 1737; ONO₂, 1632, 1288; OCO, 1660.

¹H-NMR (80 MHz) (CDCl₃): 1.48 ppm (d,3H); 1.64ppm (m,4H); 3.78ppm (g,1H); 4.08ppm (m,2H); 4.3ppm (m,2H); 7.3-7.81 (m, aromatics).

The anti-inflammatory and anti-platelet aggregation activity as well as the gastrointestinal ulcerogenicity, for instance of nitric esters having the following Mass spectrometry (i.e.): 371 (M^{+}) ; 309 $(M^{+}-0NO_{2})$; 255. formulae, were tested by means of biological studies:

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The anti-inflammatory activity of said nitric esters was determined in Wistar rats utilizing the method of E.RISLEY, G.W.NUSS, Proc. Soc. Exp. Biol. Med. 111,544 (1962), while the anti-platelet aggregation activity of said derivatives was determined on human platelets stimulated by arachidonic acid, according to the method the carrageenan paw edema, as reported in C.A.WINTER, described by V.BERTELE et al., Science 220,517 (1983).

The gastrointestainal ulcerability was evaluated by oral administration in the rat.

The anti-inflammatory and anti-platelet aggregation activity as well as the gastrointestinal ulcerability activity of said derivatives are given on Table 1, and are expressed, for each nitric ester indicated, as the power ratio relative to the corresponding acids non functionalized according to the general formula (I), according to this invention. Each value represents the mean of the values obtained by the treatment of 10 animals.

TABLE 1

COMPOUND	ANTI-INFLAM.	ANTI-AGGREG.	ANTI-INFLAM. ANTI-AGGREG. GASTROINTESTINAL
STUDIED	ACTIVITY	ACTIVITY	ULCERABILITY
(XVIII)	1,25	1,35	0,20
Ketoprofen	.	A	ч
(XII)	1,25	1,15	0,35
Flurbiprofen	n 1		Ħ
(XXIV)	1,20	1,30	0,35
Suprofen	н	7	1
(xxv)	1,05	1,25	0,30
Indobufen	1		1
(XXVI)	1,40	1,10	0,33
Etodolac	г	1	1

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In particular, the derivatives (XVIII) and (XII) submitted to additional studies of a pharmacodynamical nature have given the following results, as shown in the following examples.

- RAT CARRAGEENAN PAW EDEMA. Both compounds (XVIII) and (XII) showed an efficacy comparable with the corresponding reference drugs Ketoprofen and Flurbiprofen, the effective doses being in the 1 to 10 mg/kg p.o. range.
- RAT ADJUVANT ARTHRITIS. Animals treated for 19 consecutive days (days 3 through 21 after adjuvant injection) with 3 mg/kg p.o. of either compound (XVIII) or (XII) and their corresponding reference compound showed a significant and comparative reduction in the arthritic symptomatology compared to controls.
- MOUSE PHENYLQUINONE WRITHING. At doses ranging from 3 to 10 mg/kg p.o., compound (XVIII) and (XII) proved fully effective and their efficaciousness was almost comparable with that of the corresponding reference compounds.
- IN VIVO PLATELET AGGREGATION. While both compositions
- (XVIII) and Flurbiprofen, when administered at the dose of 20 mg/kg p. o. in the rat, inhibited collagen-induced platelet aggregation, the former (66% inhibition versus controls) was significantly more effective than the latter (40%).

BIOCHEMISTRY

- PROSTAGLANDIN SYNTHESIS IN THE INFLAMMATORY EXUDATE.

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Subcutaneous implantation of carrageenan sponge elicits

the infiltration of inflammatory cells,

as reported in , (XVIII) and

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provided the following results

GASTROINTESTINAL TOLERABILITY

were compounds Ketoprofen and Flurbiprofen at doses ranging of gastric damages already at the dose of 1 corresponding reference from 3 to 30 mg/kg p.o., both (XII) and (XVIII) compounds being significantly better tolerated than reference compounds. Ketoprofen or Flurbiprofen caused the or (XII) compounds were well damages being doseand (XII) (XVIII) tolerated even at the dose of 30 mg/kg. such studied in comparison with the RAT GASTRIC MUCOSA INJURY. of dependent, while (XVIII) severity the

to cause gastric and small intestine injury were also Similar differences in the capacity of these compounds NSAID-induced gastric GASTRIC LEUKOCYTE ADHERENCE/VESSEL DIAMETER. An early to the Using intravital microscopy, the leucokocyte adherence to mesenteric post-capillary venules could be quantified prior to and during a one hour period after the of NSAID. Unlike Ketoprofen or Flurbithe histological evaluation confirmed these findings. observed upon repeated administration of the compounds. Gastroenterology 103, 146 (1992); Trends Pharmacol. Sci. 13, 129 (1992); Am.J. Physiol. 262, G903 (1992). of leukocytes endothelium of post-capillary venules, as is the adherence pathogenesis of the administration mucosa injury event in

comparative efficacy to the corresponding reference compounds Ketoprofen and Flurbiprofen.

- GASTRIC PROSTAGLANDIN SYNTHESIS. Both compounds,

inhibited the formation of prostaglandin E2 in exudate by more than 75% compared with controls and have shown

(XII) when administered at the dose of

20 mg/kg

compounds

(1980). Both

Wature 284, 271

- CASTRIC PROSTAGLANDIN SYNTHESIS. Both compounds, (XVIII) and (XII) were studied for prostaglandin synthesis at the same doses (5-20 mg/kg p.o.) utilized for gastric injuries studies. They inhibited significantly and comparatively to the corresponding reference compounds Ketoprofen and Flurbiprofen, the synthesis of prostaglandin E2, the percent of inhibition being more than 90% at the highest dose.

released nitric oxide after their administration was plasma nitrate/nitrite 264 (XVIII) or (XII) compound, the plasma nitrate/nitrite - NO RELEASE. Evidence that compounds (XVIII) and (XII) Ketoprofen or Flurbiprofen did not affect plasma nitralevels had significantly increased by more than 50%. 85, One hour after the administration of as reported in J. Clin. te/nitrite levels significantly. ğ measurements ģ obtained evels, (1990).

Besides, additional biological studies were performed on derivatives (XII) and (XVIII); said studies have

profen, (XVIII) or (XII) did not induce significant

leukocyte adherence, while increasing the diameter of vessels significantly. No changes in blood pressure were observed.

GENERAL PHARMACOLOGY

A secondary pharmacological evaluation of compound (XVIII) or (XII) was performed in comparison with Ketroprofen or Flurbiprofen. No relevant additional adverse reactions were observed affecting the central nervous, autonomic, cardiovascular, respiratory and gastrointestinal systems.

TOXICOLOGY

- ACUTE TOXICOLOGY IN RODENTS.

The acute toxicity of said derivatives (XVIII), (XXIV), (XXIV), (XXI) and (XXVI) was then evaluated by p.o. administration of a single dose of each compound (XVIII), (XXIV), (XXII) and (XXVI), utilizing, for each derivative, groups of 10 Swiss mice. Death incidence and the onset of toxic symptoms were reported for a period of 14 days.

Even after administration of a dose of 100 mg/kg of each compound (XVIII), (XXIV), (XXV), (XII) and (XXVI), no apparent toxicity symptoms were noticed in the animals studied.

In particular, preliminary studies on compounds (XVIII) or (XII) were performed in the mouse by two administration routes. No evident toxicity was observed in the animals treated with oral or intraperitoneal doses of

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300 mg/kg of either compound.

- MAXIMUM TOLERATED DOSE IN NON RODEWTS. Preliminary studies indicate that compounds (XVIII) and (XII) were very well tolerated in this animal species that is known to be particularly sensitive to this class of compounds. The animals were administered increasing oral doses up to 30 mg/kg of either compound and no apparent symptoms were observed, while the reference compounds Ketoprofen and Flurbiprofen, administred at the dose of 10 mg/kg caused the death of the animals.

CLAIMS

1. Nitric esters characterized in that they have the following general formula:

where:

substituted or non substituted alkyl chains, R is A and B are chosen among hydrogen, linear or branched, chosen among:

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 R_2 is chosen among hydrogen, methyl, ethyl, alkyl Y is chosen among oxygen, NH, NR $_{
m 1}$, where R $_{
m 1}$ is a linear or branched alkyl chains linear or branched by 3 to 12 carbon atoms, group, and n is comprised between 1 and 10. substituted or non substituted,

2. Nitric ester according to claim 1, characterized in that R is:

(IV)

 $R_{\rm 2}$ is equal to methyl, A and B are equal to hydrogen, Y is equal to oxygen and n is equal to four.

3. Nitric ester according to claim 1, characterized in that R is equal to:

 R_2 is equal to methyl, Y is equal to oxygen, A and B are equal to hydrogen and n is equal to four. 4. Nitric ester according to claim 1, characterized in that R is equal to:

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 R_{2} is equal to methyl, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four. 5. Nitric ester according to claim 1, characterized in that R is equal to:

 R_{2} is equal to ethyl, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four. 6. Nitric ester according to claim 1, characterized in that R is equal to:

(VIII)

 R_{2} is equal to hydrogen, A and B are equal to hydrogen,

Y is equal to oxygen, and n is equal to four.

7. Nitric esters according to claim 1, characterized in that they are utilizable in pharmaceutics as anti-

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inflammatory agents.

8. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of rheumatic diseases, disorders of immunologic nature, and slightmiddle severity painful conditions. 9. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of diseases affecting the cardiovascular system, the treatment of miocardial and brain ischemiae and in cases of arterial thromobosis as platelet anti-aggregation agents. 10. Process for the preparation of nitric esters according to claim 1 and having the following general formu-1a:

where A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among:

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(IXX)

 R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, Y is chosen among Oxygen, NH, NR_{l} , where R_{l} is a linear or branched alkyl chain, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

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- Preparation of sodium salt of derivatives having the following general formula:

where R is chosen among the following structures:

(II), (III), (IV), (VI), (VII), (VIII), (X), (XXI), (XXXV), or preparation of derivatives (XIV) functionalized to the carboxylic group as acilic chlorides, anhydrides or - Reaction between the sodium salt of said derivatives (XIV) or of said derivatives (XIV) functionalized to the carboxylic group, with a compound having the following general formula:

(X

where:

 $R_{f 4}$ is chosen among chlorine, bromine, NHR $_{f 6}$, with R $_{f 6}$ hydrogen linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted

ween 1 and 10, obtaining the relative monomeric esters or non substituted alkyl chains, R₃ is chosen among chlorine, bromine and iodine, and n is comprised betor the relative amides; - Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, obtaining nitric esters of derivatives (I). 11. Process for the preparation of nitric esters according to claim 1 and having the following general formu-

substituted or non substituted alkyl chains, R₂ is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted A and B are chosen among hydrogen, linear or branched, or non substituted, R is chosen among:

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$$H_3C \longrightarrow C_2 H_3 \qquad (WIII)$$

$$H_3C \longrightarrow C_2 H_3 \qquad (XXXV)$$

$$C_1 \longrightarrow C_2 H_3 \qquad (XXXV)$$

$$C_2 \longrightarrow C_3 H_3 \qquad (XXXV)$$

$$C_3 \longrightarrow C_3 \longrightarrow C_3 H_3 \qquad (XXXV)$$

or branched alkyl group, and n is comprised between 1 Y is chosen among oxygen, NH, NR $_{1}$, where R $_{1}$ is a linear and 10, characterized in that it comprises the following steps:

(XXI)

- Preparation of sodium salt of derivatives having the following general formula:

(II), (III), (IV), (VI), (VII), (VIII), (X), where R is chosen among the following structures:

(xxx), (xxxv),

to the caboxylic R_2 is chosen among hydrogen, methyl, ethyl, alkyl or preparation of group, such as acilic chlorides, anhydrides and the chains linear or branched by 3 to 12 carbon atoms, derivatives (XIV) functionalized substituted or non substituted, 11ke; - Reaction between the sodium salt of said derivatives (XIV) or of said derivatives (XIV) functionalized to the carboxylic group, with a compound having the following general formula:

where:

 $\mathtt{R_4}$ is chosen among chlorine, bromine, NHR $_6$, with $\mathtt{R_6}$ hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, obtaining the relative monomeric esters or the relative amides; - Reaction of said monomeric esters or said amides with obtaining said monomeric esters or said amides, characan halogenating compound such as PB $\mathbf{r_{3}}$ or the like, terized by the presence of a terminal halogen group;

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- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group with a nitrating agent such as $AgNO_3$ or the like, obtaining nitric esters of derivatives (I).

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INTERNATIONAL APPLICATION PUBLISH		ON TRE
(51) International Patent Classification 5:		(11) International Publication Number: WO 94/12463
COTC 203/04, A61K 31/21, COTD 333/22, A1 209/46, 491/04, A61K 31/04, 31/38, COTD 207/337, 209/88, 333/24, A61K 31/16, COTC 235/78, 235/34, 233/21		(4) Laternational Publication Date: 9 June 1994 (19.06.94)
(21) International Application Number: PCT/EP93/03193	3,03193	(81) Designated Status: AU, BR, CA, CZ, FI, HU, JP, KP, KR, NO, ND, NZ, PL, RO, RU, SK, UA, US, European patent (AT, BR, CH, DP, DK, ES, FR, GR, GR, ET, II, LU, MC, NL.
Š	E	P1, SE). Published With international search report.
(71) Appleant (for all derignated Scatts except US); HCT-HEALTH CARE TRADING LTD. (IE/IE); Dame Street, Dublin 2- (IE).	EALTH Jublin 2	
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(54) THE: NITRIC ESTERS HAVING A PHARMACOLOGICAL ACTIVITY AND PROCESS FOR THEIR PREPARATION

(57) Abstract

Nitric esters with pharmacological activity laving general formula (I), their pharmaceutical utilisation and process for their preparation.

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NITRIC ESTERS HAVING A PHARMACOLOGICAL ACTIVITY AND PROCESS FOR THEIR PREPARATION

Object of the present invention are nitric esters with an anti-inflammatory and/or anti-platelet aggregation activity, their pharmaceutical utilization and process for their preparation.

PRIOR ART

Some derivatives of propionic acid, such as for instancommonly known as ketoprofen, have been used for a long time as pharactivity and are sold on the different international maceutical preparations for their anti-inflammatory markets since many years. The process for the prepara-2-(3-benzoylphenyl)propionic acid has been corresponding to the US patent 3,641,127; in the French PINNA et al., FARMACO Ed. Sci. 35,684 (1980); while the et al., Eur.J.Clin. Pharmacol. 18,407 (1980). The use described in the South African patent n° 68 00,524, patent n° M6444 and also in C.A. 75,5528m (1971); G.A. pharmacokinetics in humans is described in T. ISHIZAKI ce, keptofren, as well as the use of other products which are utilized as anti-inflammatory agents, involves, as known, severe adverse reactions, for instance of derivatives of propionic acid, such as, for instanpossible in the gastrointestinal apparatus, as well as ce 2-(-3-benzoylphenyl)propionic acid, damages to the liver and the kidneys. of

MONCADA, Reviews, There is much experimental evidence [S. Pharmacological R.M.J. PALMER, E.A.HIGGS,

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 $^{\mathrm{Z.YANG}}$, Hypertension, 19,117 (1992)], on whose basis the integrity of vasal endothelium is thought to be a 43(2), 109 (1991); T.H.LUSHER, C.M.BOULANGER, Y.DOHI, basic barrier against the onset of pathological processes in several organs and apparatuses. Such protection barrier, and therefore the integrity of the vasal endothelium, is ensured physiologically by the presence of nitric oxide and prostacyclin. The treatment with non steroid drugs having an antiinflammatory activity, such as, for instance, 2-(3benzoylphenyl)propionic acid or ketoprofen, causes the inhibition of cyclo-oxygenase, an enzyme which syntesizes the precursor of prostacyclin.

prostacyclin, the reserve of same in the tissues is As a consequence, having so inhibited the production of markedly depauperated, and therefore the integrity of vasal endothelium is compromised.

reduction of prostacyclin, diffuse pathological process As said, because of this endothelial damage due to the break out which affect the gastrointestinal apparatus, liver and kidneys.

OBJECTS OF THE INVENTION

Object of the present invention is that to provide a group of products which, while ensuring the maintenance of the pharmacological activity characteristic of the known anti-inflammatory agents, are capable of eliminating the adverse reactions caused by the treatment with

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said agents.

Another object of the present invention is the realization of a process for the preparation of a group of products having an anti-inflammatory activity while being exempt from the adverse reations which are typical of anti-inflammatory agents.

DESCRIPTION OF THE INVENTION

These and still other objects and associated advantages which will appear from the following description, are obtained with nitric esters having the following general formula:

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where:

substituted or non substituted alkyl chains, R is A and B are chosen among hydrogen, linear or branched, chosen among

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is chosen among hydrogen, methyl, ethyl, alkyl non substituted, Y is chosen among chains linear or branched by 3 to 12 carbon atoms, oxygen, NH, N $_{
m I}$, where $_{
m I}$ is a linear or branched alkyl group and n is comprised between 1 and 10. substituted or

In fact, it has been observed that the introduction of group such as a terminal nitric ester in the general logical activity characteristic of non steroid antiformula derivatives (I) allows to mantain the pharmacoinflammatory agents, while eliminating the adverse reactions caused by the treatment with such agents.

Besides, it has been observed that derivatives (I) are useful also in the treatment of various morbide conditions, such as, for instance, rheumatic diseases in general, disoders of immunologic nature, and can also assuage light-middle severity painful conditions of any

More still, the derivatives (I) subject matter of this invention, are useful in the treatment of diseases of the cardio-vascular apparatus, and in particular in the treatment of miocardial and brain ischemiae as well as in artery thrombosis as anti-platelet agents. Always according to this invention, a nitric ester of general formula (I) proved particularly advantageous,

hydrogen is chosen as A and B, methyl is chosen as $\mathtt{R_2}$,

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and as R is chosen

(IV

oxygen is chosen as y and n is equal to four, according to the following formula:

Also particularly advantageous according to this invention is the nitric ester of a general formula (I)

hydrogen is chosen as A and B, as R is chosen

(XI)

methyl is chosen as R_2 oxygen is chosen as Y and n is equal to four, according to the following formula:

particularly advantageous are the nitric esters of Still more, always according to the present invention, general formula derivatives (I) where:

hydrogen is chosen as A and B, as R are chosen

(II)

(VI)

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(VIII)

methyl, ethyl and hydrogen are chosen as $\mathtt{R_2}$, oxygen is chosen as y and n is equal to four, according to the following formulae:

$$\begin{pmatrix} 0 & CH_{2} & CH_{3} & CH_{4} & CH_{4} & CH_{4} & CH_{4} & CH_{5} & CH_{$$

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For the preparation of general formula nitric esters

(I), subject matter of the present invention, particularly advantageous proved to be a first process which, according to the invention, comprises the following steps:

 Preparation of the sodium salt of the products having the following general formula:

(XIV)

where R₂ is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, R is chosen among: (II), (III), (IV), (VI), (VII), (VIII), (IX), (X), (XXX)

or preparation of derivatives (XIV) functionalized to the carboxyl group, such as acilic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (XIV) or between said derivatives (XIV) functionalized to the carboxylic group, with a composition having the following general formula:

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R_—(C),—R3

(XV)

where

R₄ is chosen among chlorine, bromine, NHR₆ with R₆ chosen among hydrogen, lineal or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R₃ is chosen among chlorine, bromine, and iodine, and n is comprised between 1 and 10, obtaining in this way the relative monomeric esters or the relative amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, obtaining in this way nitric esters of derivatives (I).

Also a second process proved to be particularly advantageous which, always according to the present invention, comprises the following steps:

 Preparation of the sodium salt of derivatives having the following general formula:

(XIV)

where R is chosen among:

(II), (III), (IV), (VI), (VII), (VIII), (X), (XXX), (XXXV) R₂ is chosen among hydrogen, methyl, ethyl, alkyl preparation of derivatives (XIV) functionalized to the carboxylic group, such as acidic chlorides, anhydrides chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, or, alternatively, or the like; - Reaction between the sodium salt of said derivatives (XIV) or between said derivatives (XIV) functionalized to the carbboxylic group, with a composition having the following general formula:

 R_{4} is chosen among chlorine, bromine, NHR $_{6}$ with R_{6} substituted or non substituted alkyl chains, and n is equal to hydrogen, or linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, comprised between 1 and 10, obtaining in this way the relative monomeric esters or amides;

- Reaction of said monomeric esters or said amides with

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obtaining in this way said monomeric esters or said a terminal an halogenating composition such as PBr_3 or the like, amides characterized by the presence of halogen group;

characterized by the presence of a terminal halogen group, with a nitrating agent such, as AgNO₃ or the - Reaction of said monomeric esters or said amides like, obtaining in this way nitric esters of derivatiThe solvents utilized in the processes subject matter form, methylene chloride, acetonitrile, dimethylformaof this invention are preferably chosen among chlorotetrahydrofuran, 1,4-dioxane and the like.

subject matter of this invention, consist of a limited number of steps, allowing to obtain the products which derive from said processes in a short time and with The processes for the preparation of derivatives (I) satisfactory yields even on the industrial plane.

According to the processes subject matter of this invention, the preparation of a nitric ester having the following formula:

red as described in the following example, given as a mere indication without limiting the protection scope proved to be particularly advantageous, which is prepaof this invention.

EXAMPLE 1

a) 2 g of 2-fluoro-alpha-methyl-4-diphenylacetic acid for 5 minutes, then the solvent was evaporated under were added to a solution constituted by 10 ml of methyl stirred reduced pressure, obtaining the sodium salt of 2-fluoalcohol and 0.23 g of Na. The reaction mix was ro-alpha-methyl-4-diphenylacetic acid.

lacetic acid obtained in this way was suspended in 20 b) The sodium salt of 2-fluoro-alpha-methyl-4-dipheniml of dimethylformamide and 3 ml of 1,4-dibromo-butane were added by dripping to this suspension. The reaction mix was stirred for 22 hours at room temperature, then the NaBr which had formed was filtered and the solvent was evaporated under reduced pressure. The residue so obtained was treated with methylene chloride and, after elimination by filtration of the insoluble residue, the re, obtaining 3 g of a dry residue which was purified methylene chloride was evaporated under reduced pressuby silica gel chromatography, utilizing an eluent mix constituted by hexane/methylene chloride 1/1 (V/V).

The head fractions were collected, the solvent was 5fluoro-alpha-methyl-4-diphenylacetate of 4-bromobutyl evaporated under reduced pressure and 1.86 g of

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(XXII) were obtained

IR (cm⁻¹): C=0,1470

1-H-NMR (300 MHz) (CDCl3) : 1.51ppm (d,3H); 1.56ppm (m,4H); 3,35ppm (t,2H); 3.61ppm (g,1H); 4.1ppm (t,2H); 7.3-7.55 (s, 1H); (m,1H); 7.17ppm 7.05ppm

c) 1.2 g of AgNO $_{
m 3}$ dissolved in 8.3 ml of acetonitrile reaction mix was stirred for 48 hours at room temperature and then filtered. The solvent was evaporated from the resulting solution under reduced pressure, obtaias described acetonitrile. The ning a residue which was treated with methylene chroride. The mix obtained in this way was filtered again and organic phase was purified by silica gel pressure chromatography, utilizing an eluent mix constituted by diethylether/hexane $3/7 \ (V/V)$. The fractions containing the products were collected, the solvent was evaporated under reduced pressure and 1.2 g of nitric ester of 2fluoro-alpha-methyl-4-diphenyl acetate of 4-hydroxybuwere added to 1.86 g of (XXII), obtained inder b) dissolved in 7.5 ml of tyl (XII) were obtained.

 $IR(cm^{-1}): C=0,1737; ONO_2, 1623, 1274.$

(d,3H); 1.72ppm (t,2H); (m,4H); 3.74ppm (q,1H); 4.13 ppm (t,2H); 4.4ppm 7.13ppm (t,2H, aromatics); 7.32-7.42ppm (m,4H, (CDC1₃): 1.53ppm tics); 7.53ppm (m,2H, aromatics). ¹H-NMR (300 MHz)

Mass spectrometry (i.e.): (M⁺)361; (M+1-NO₂)316; 243;

199.

Always according to the processes subject matter of the a nitric present invention, also the preparation of ester having the following formula:

proved particularly advantageous, which is prepared as described in the example shown hereunder, given as a mere indication without limiting the protection scope of this invention.

EXAMPLE 2

a) 10 g of 2-(3-benzoilphenyl)propionc acid were added minutes, then the solvent was evaporated under reduced pressure, obtaining a residue constituted by the sodium to a solution constituted by 80 ml of methyl alcohol stirred salt of 2-(3-benzoilphenyl)propionic acid. and 1.19 g of Na. The reaction mix was

mo-butane were added to the residue obtained in this temperature and then the solvent was evaporated under b) 100 ml of dimethylformamide and 28.1 g of 1,4-dibroway. The reaction mix was kept for 24 hours at room reduced pressure. 40 ml of water and 60 ml of methylene

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and the organic phase was extracted and anhydrified on was evaporated under chloride were added to the residue obtained in this way reduced pressure until a dry residue was obtained. the solvent sodium sulphate and

ted, the solvent was evaporated under reduced pressure The residue was purified by silica gel chromatography, diethyl sther/hexane 1/1 (V/V). The head fractions were collecand 8.8 g of 2-(3-benzoilphenyl)propionate of 4-bromo-ል constituted mix butyl (XXIII) were obtained. eluent an utilizing

'H-NMR(200MHz) (CDCl₃): 1.53ppm (d,3H); 1.84ppm (m,4H); 3.32ppm (t,2H); 3.78ppm (q,1H); 4.09ppm (t,2H); 7.27 (m,1H, aromatics); 7.38-7.99 (m,8H aromatics).

c) 5.5 g of AgNo, dissolved in 38 ml of acetonitrile were added to 8.8 g of (XXIII) obtained as described under b) dissolved in 35 ml of acetonitrile. The reaction mix was stirred for 24 hours at room temperature Mass spectometry (i.e.): 388 (M⁺); 309 (M⁺-Br); 209.

and, having added 1.76 g of AgNO $_3$, the reaction mix was stirred for 24 more hours at room temperature and then filtered. The solvent was evaporated from the resulting a residue obtaining which was treated with methylene chloride. solution under reduced pressure,

The mix obtained in this way was filtered again and the pressure chromatography, utilizing an eluent mix constituted by gel silica organic phase was purified by ethyl ether/hexane 3/7 (V/V).

The fractions containing the product were collected, the solvent was evaporated under reduced pressure and 3.4 g of nitric ester of 2-(3-benzoilphenyl)propionate of 4-hydroxybutyl (XVIII) were obtained.

IR (cm⁻¹): C=0 1737; ONO₂, 1632, 1288; OCO, 1660.

1H-NMR (80 MHz) (CDCl₃): 1.48 ppm (d,3H); 1.64ppm (m,4H); 3.78ppm (q,1H); 4.08ppm (m,2H); 4.3ppm (m,2H); 7.3-7.81 (m, aromatics). Mass spectrometry (i.e.): 371 (M⁺); 309 (M⁺- $0NO_2$); 255. The anti-inflammatory and anti-platelet aggregation activity as well as the gastrointestinal ulcerogenicity, for instance of nitric esters having the following formulae, were tested by means of biological studies:

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$$C_2H_3 = \begin{cases} C_2H_3 & -CONO_2 \\ C_2H_3 & -CONO_2 \\ C_2H_3 & CONO_2 \end{cases}$$
(XXVI)

The anti-inflammatory activity of said nitric esters was determined in Wistar rats utilizing the method of the carrageenan paw edema, as reported in C.A.WINTER, E.RISLEY, G.W.NUSS, Proc. Soc. Exp. Biol. Med. 111,544 (1962), while the anti-platelet aggregation activity of said derivatives was determined on human platelets stimulated by arachidonic acid, according to the method described by V.BERTELE et al., Science 220,517 (1983).

power ratio relative to the corresponding acids non The anti-inflammatory and anti-platelet aggregation activity of said derivatives are given on Table 1, and according to this invention. Each value represents the activity as well as the gastrointestinal ulcerability are expressed, for each nitric ester indicated, as the functionalized according to the general formula (I), mean of the values obtained by the treatment of animals.

TABLE 1

OUND ANTI-INFLAM. ANTI-AGGREG. GASTROINTESTINAL	DIED ACTIVITY ACTIVITY ULCERABILITY	VIII) 1,25 1,35 0,20	oprofen 1 1 1	XII) 1,25 1,15 0,35	1 1	IV) 1,20 1,30 0,35	rofen 1 1 1	XV) 1,05 1,25 0,30	obufen 1 . 1 _ 1	01) 1,40 1,10 0,33	dolar.
COMPOUND	STUDIED	(XVIII)	Ketoprofen	(XII)	Flurbiprofen	(XXIV)	Suprofen	(xxv)	Indobufen	(XXVI)	Etodolac

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as shown in mitted to additional studies of a pharmacodynamical In particular, the derivatives (XVIII) and (XII) subnature have given the following results, the following examples.

- RAT CARRAGEENAN PAW EDEMA. Both compounds (XVIII) and (XII) showed an efficacy comparable with the corresponding reference drugs Ketoprofen and Flurbiprofen, the effective doses being in the 1 to 10 mg/kg p.o. range.
- (XII) and their corresponding reference compound showed cutive days (days 3 through 21 after adjuvant injection) with 3 mg/kg p.o. of either compound (XVIII) or a significant and comparative reduction in the arthri-- RAT ADJUVANT ARTHRITIS. Animals treated for 19 consetic symptomatology compared to controls.
- · MOUSE PHENYLQUINONE WRITHING. At doses ranging from 3 to 10 mg/kg p.o., compound (XVIII) and (XII) proved fully effective and their efficaciousness was almost comparable with that of the corresponding reference compounds.
- IN VIVO PLATELET AGGREGATION. While both compositions
- (XVIII) and Flurbiprofen, when administered at the tion versus controls) was significantly more effective induced platelet aggregation, the former (66% inhibidose of 20 mg/kg p. o. in the rat, inhibited collagenthan the latter (40%).

BIOCHEMISTRY

- PROSTAGLANDIN SYNTHESIS IN THE INFLAMMATORY EXUDATE.

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hesis at the same doses (5-20 mg/kg p.o.) utilized for (XVIII) and (XII) were studied for prostaglandin syntgastric injuries studies. They inhibited significantly COMpounds Ketoprofen and Flurbiprofen, the synthesis of prostaglandin E2, the percent of inhibition being more GASTRIC PROSTAGLANDIN SYNTHESIS. Both compounds, corresponding reference than 90% at the highest dose. and comparatively to the

264 - NO RELEASE. Evidence that compounds (XVIII) and (XII) released nitric oxide after their administration was One hour after the administration of either (XVIII) or (XII) compound, the plasma nitrate/nitrite plasma nitrate/nitrite Ketoprofen or Flurbiprofen did not affect plasma nitralevels had significantly increased by more than 50%. Invest., 85, J. clin. te/nitrite levels significantly. measurements of as reported in ģ obtained levels, (1990).

Besides, additional biological studies were performed derivatives (XII) and (XVIII); said studies have

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provided the following results.

GASTROINTESTINAL TOLERABILITY

onset of gastric damages already at the dose of 3 GASTRIC MUCOSA INJURY. (XVIII) and (XII) were compounds Ketoprofen and Flurbiprofen at doses ranging studied in comparison with the corresponding reference (XVIII) COMpounds being significantly better tolerated than reference compounds. Ketoprofen or Flurbiprofen caused the mg/kg, the severity of such damages being dosedependent, while (XVIII) or (XII) compounds were well and tolerated even at the dose of 30 mg/kg. (XII) from 3 to 30 mg/kg p.o., both RAT

Similar differences in the capacity of these compounds to cause gastric and small intestine injury were also event in the pathogenesis of NSAID-induced gastric - GASTRIC LEUKOCYTE ADHERENCE/VESSEL DIAMETER. An early is the adherence of leukocytes to the post-capillary venules, as reported in Using intravital microscopy, the leucokocyte adherence fied prior to and during a one hour period after the The histological evaluation confirmed these findings. observed upon repeated administration of the compounds. (1992); Trends Pharmacol. Sci. 13, 129 (1992); Am.J. Physiol. 262, G903 (1992). to mesenteric post-capillary venules could be quantiadministration of NSAID. Unlike Ketoprofen or Flurbiprofen, (XVIII) or (XII) did not induce significant Gastroenterology 103, 146 endothelium of injury

leukocyte adherence, while increasing the diameter of vessels significantly. No changes in blood pressure were observed.

GENERAL PHARMACOLOGY

A secondary pharmacological evaluation of compound (XVIII) or (XII) was performed in comparison with Ketroprofen or Flurbiprofen. No relevant additional adverse reactions were observed affecting the central nervous, autonomic, cardiovascular, respiratory and gastrointestinal systems.

FOXICOLOGY

- ACUTE TOXICOLOGY IN RODENTS.

The acute toxicity of said derivatives (XVIII), (XXIV), (XXV), (XII) and (XXVI) was then evaluated by p.o. administration of a single dose of each compound (XVIII), (XXIV), (XII) and (XXVI), utilizing, for each derivative, groups of 10 Swiss mice. Death incidence and the onset of toxic symptoms were reported for a period of 14 days.

Even after administration of a dose of 100 mg/kg of each compound (XVIII), (XXIV), (XXV), (XII) and (XXVI), no apparent toxicity symptoms were noticed in the animals studied.

In particular, preliminary studies on compounds (XVIII) or (XII) were performed in the mouse by two administration routes. No evident toxicity was observed in the animals treated with oral or intraperitoneal doses of

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300 mg/kg of either compound.

- MAXIMUM TOLERATED DOSE IN NON RODENTS. Preliminary studies indicate that compounds (XVIII) and (XII) were very well tolerated in this animal species that is known to be particularly sensitive to this class of compounds. The animals were administered increasing oral doses up to 30 mg/kg of either compound and no apparent symptoms were observed, while the reference compounds Ketoprofen and Flurbiprofen, administred at

the dose of 10 mg/kg caused the death of the animals.

CLAIMS

1. Nitric esters characterized in that they have the following general formula:

substituted or non substituted alkyl chains, R is A and B are chosen among hydrogen, linear or branched, chosen among:

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Y is chosen among $R_{
m 2}$ is chosen among hydrogen, methyl, ethyl, alkyl oxygen, NH, NR $_{
m l}$, where R $_{
m l}$ is a linear or branched alkyl chains linear or branched by 3 to 12 carbon atoms, group, and n is comprised between 1 and 10. substituted or non substituted,

2. Nitric ester according to claim 1, characterized in that R is:

(IV)

 R_{2} is equal to methyl, A and B are equal to hydrogen, Y is equal to oxygen and n is equal to four.

3. Nitric ester according to claim 1, characterized in that R is equal to:

 R_2 is equal to methyl, Y is equal to oxygen, A and B are equal to hydrogen and n is equal to four.

4. Nitric ester according to claim 1, characterized in that R is equal to:

2,7

(11)

 $R_{\rm 2}$ is equal to methyl, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

5. Nitric ester according to claim 1, characterized in that R is equal to:

 $\rm R_2$ is equal to ethyl, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

 Nitric ester according to claim 1, characterized in that R is equal to:

(IIIA)

 R_{2} is equal to hydrogen, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

7. Nitric esters according to claim 1, characterized in that they are utilizable in pharmaceutics as anti-

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inflammatory agents.

8. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of rheumatic diseases, disorders of immunologic nature, and slightmiddle severity painful conditions.

9. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of diseases affecting the cardiovascular system, the treatment of miocardial and brain ischemiae and in cases of arterial thromobosis as platelet anti-aggregation agents.

10. Process for the preparation of nitric esters according to claim 1 and having the following general formu-

la:

where A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among:

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 R_2 is chosen among hydrogen, methyl, ethyl, alkyl substituted or non substituted, Y is chosen among Oxygen, NH, NR $_{
m l}$, where $_{
m R}_{
m l}$ is a linear or branched alkyl chains linear or branched by 3 to 12 carbon atoms, chain, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

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- Preparation of sodium salt of derivatives having the following general formula:

(XIX)

where R is chosen among the following structures:

(II), (III), (IV), (VI), (VII), (VIII), (IX), (X), (XXI), (XXXV), or preparation of derivatives (XIV) functionalized to the carboxylic group as acilic chlorides, anhydrides or the like; - Reaction between the sodium salt of said derivatives (XIV) or of said derivatives (XIV) functionalized to the carboxylic group, with a compound having the following general formula:

(X

hydrogen linear or branched alkyl chain, A and B are $R_{f 4}$ is chosen among chlorine, bromine, NHR $_{f 6}$, with $R_{f 6}$ chosen among hydrogen, linear or branched, substituted

or non substituted alkyl chains, $\mathbf{R}_{\mathbf{J}}$ is chosen among chlorine, bromine and iodine, and n is comprised between 1 and 10, obtaining the relative monomeric esters or the relative amides; - Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, obtaining nitric esters of derivatives (I). 11. Process for the preparation of nitric esters according to claim 1 and having the following general formu-

chosen among hydrogen, methyl, ethyl, alkyl chains substituted or non substituted alkyl chains, R_2 is linear or branched by 3 to 12 carbon atoms, substituted A and B are chosen among hydrogen, linear or branched, or non substituted, R is chosen among:

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$$H_{3}C = \begin{pmatrix} V_{11} & V_{12} & V_{111} \\ V_{12} & V_{13} & V_{14} \\ V_{14} & V_{15} & V_{14} \\ V_{15} & V_{15} & V_{15} \\ V_{15}$$

Y is chosen among oxygen, NH, NR_1 , where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

(XXI)

- Preparation of sodium salt of derivatives having the following general formula:

where R is chosen among the following structures:

(II), (III), (IV), (VI), (VII), (VIII), (X), (X), (XXI), (XXXV),

or preparation of to the caboxylic R₂ is chosen among hydrogen, methyl, ethyl, alkyl group, such as acilic chlorides, anhydrides and the chains linear or branched by 3 to 12 carbon atoms, derivatives (XIV) functionalized substituted or non substituted, like; - Reaction between the sodium salt of said derivatives (XIV) or of said derivatives (XIV) functionalized to the carboxylic group, with a compound having the following general formula:

(XVI)

where:

 $R_{f 4}$ is chosen among chlorine, bromine, NHR $_{f 6}$, with $R_{f 6}$ hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, obtaining the relative monomeric esters or the relative amides; - Reaction of said monomeric esters or said amides with obtaining said monomeric esters or said amides, characan halogenating compound such as PB ${f r}_3$ or the like, terized by the presence of a terminal halogen group;

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- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group with a nitrating agent such as $AgNO_3$ or the like, obtaining nitric esters of derivatives (I).

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